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STUDIES ON THE CONDITIONS OF ACTIVITY IN
ENDOCRINE GLANDS

XV. PSEUDAFFECTIVE MEDULLIADRENAL SECRETION

BY

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From the Laboratories of Physiology in the Harvard Medical School

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STUDIES ON THE CONDITIONS OF ACTIVITY IN ENDOCRINE GLANDS

XV. PSEUDAFFECTIVE MEDULLIADRENAL¹ SECRETION

W. B. CANNON AND S. W. BRITTON²

From the Laboratories of Physiology in the Harvard Medical School

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The bodily reactions attending great emotional excitement are elemental. In many respects they are common to man and to lower animals of the vertebrate series. They involve changes which may be regarded as instinctive adjustments to critical situations, and as directed toward self preservation. They may dominate behavior. They may thoroughly disturb beneficent functions, such as secretion and digestion. A method which will permit the securing of further insight into emotional reactions is therefore important.

The student of emotional reactions is confronted by almost insuperable difficulties. In order to study intimately the changes associated with great excitement it is necessary to examine as exactly as possible the functioning of various organs or systems of organs in the body. This often cannot be done at all unless the animal is subjected to anesthesia. So far as emotion is concerned, anesthesia, of course, promptly obliterates the very responses which are the object of study. But even under circumstances in which anesthesia would not be required there is frequently trouble in establishing consistently the emotional states which we wish to study. The natural antagonism between two laboratory animals, the dog and the cat, has been used to induce an emotional reaction. The excite-

¹ The functional separability of the adrenal cortex and the adrenal medulla emphasizes the importance of using terms to apply to each portion of the adrenal body that will distinguish between them. One may use the expression "medulla of the adrenal gland" or the "adrenal medulla" to discriminate that portion from the gland as a whole. The latter expression is clear, but unfortunately does not yield an adjective form. As a means of indicating briefly and distinctly the part of the adrenal structure which is under consideration, I propose, at the suggestion of Prof. E. K. Rand of the Department of Latin, Harvard University, that the adrenal medulla be referred to as the "medulliadrenal gland" and that the cortex be referred to as the "corticadrenal gland."

² Medical Fellow of the National Research Council.

ment produced by confronting these two animals is likely, however, to be temporary, for a disturbance which at first may be marked becomes gradually less pronounced as the animals grow accustomed to each other. Again, during the brief period of the reaction opportunity to make careful observations can hardly be obtained, and furthermore such measures as may be taken for studying the response may interfere disastrously with the response itself.

The possibility of obtaining deeper insight into the physiological aspects of emotional excitement is suggested by previous proof that central mechanisms for emotional reactions can be artificially activated in the decerebrate animal, and also by evidence that the thalamic region plays an important rôle as a center for emotional expression. In 1904 Woodworth and Sherrington (1) described certain phenomena which could be called forth from the background of decerebrate rigidity. These phenomena resembled the expression of emotional states, and were designated "pseudoaffective reflexes." In Sherrington's words, "The truncation of the brain of the mammal at the mesencephalon annihilates the neural mechanism to which the affective psychosis is adjunct. But it leaves fairly intact the reflex motor machinery whose concurrent action is habitually taken as an outward expression of an inward feeling." These quasi-emotional reactions, induced by stimulating an afferent nerve, included movements of the limbs as in progression, turning of the head and neck toward the points stimulated, opening the mouth, retraction of the lips and tongue, movement of the vibrissae, snapping of the jaw, lowering of the head, opening of the eye lids, dilatation of the pupils, snarling or plaintive vocalization and a transient increase of arterial blood pressure. The reactions appeared not only in combination but sometimes singly or in small combinations. Bazett and Penfield (2) have reported that in the "chronic" decerebrate cat the pseudoaffective phenomena are more developed after the first few days than immediately after operation, and that in addition to the activities listed by Sherrington they noted lashing of the tail, protective movements of the fore limbs, kicking and biting and in some cases growling.

Hughlings Jackson (3) and Head (4) have pointed out that the nervous system is organized in a neural hierarchy such that primitive reactions, which might otherwise disturb the more discriminative responses of higher levels, are by these repressed. The rigidity of the decerebrate preparation may thus be explained as due to the "release" of a neuro-muscular apparatus that is normally kept under dominance of the cerebrum. That the pseudoaffective phenomena described above can be made to intrude upon the rigidity indicates that a neural mechanism for these phenomena is present in the nervous system below the pons. That they do not manifest themselves unless evoked by special excitation indicates that the mech-

anism involved, though released from cerebral control, is itself suppressed by or subordinated to the apparatus that is active in maintaining rigidity.

The thalamic region comprises a group of centers which, in the lower vertebrate, lacking a cerebral cortex, serve the primitive functions for maintaining existence. These centers, though normally under the inhibitory control of the cortex, are capable of energetic response when conditions demand urgent and impulsive action. If the cortical government is set aside the subordinate activities become prominent. Goltz's (5) hemisphereless dog and Barenne's (6) cats deprived of the neopallium are cases in point. Even to conditions which are ordinarily agreeable the animals reacted by signs of rage. The dog barked, snapped and struggled vigorously when taken by his keeper to be fed, and the cats when lifted up growled and hissed—i.e., their reactions were part of the well-known complex for resistance or defense. In human cases, likewise, as Head and Holmes (7) have noted, such damage to the brain as isolates the thalamus from the cortex has as its most remarkable feature "an excessive response to affective stimuli." Removal of the cortex in an acute experiment might, therefore, permit the activity of these lower centers to appear, and to prevail over the rigidity which usually masks them when the mid-brain is transected. Typical and stereotyped behavior should then occur, such as may be natural in attack or defence. Indeed, just those mechanisms might be brought into action that operate during the instinctive efforts of animals to escape from danger or to fight for existence. In that case the well-known visceral accompaniments of these instinctive acts might reasonably be expected to be present.

The foregoing ideas suggest the possibility of obtaining a preparation in which the basal ganglia, freed from the dominance of the cortex, might function in a manner which would exhibit many of the physiological phenomena attending intense emotional disturbance. Destruction of the cortex would eliminate an essential factor for sensation; and therefore the use of an anesthetic, which would disturb not only nervous but probably other functions, could be dispensed with. The absence of the higher inhibiting centers would permit a *prolonged* exhibition of the quasi-emotional phenomena. These phenomena could be studied experimentally during the period without any chance of interrupting the relatively simple automatic activities. The methods used in the study of such a preparation and the results obtained from it might then be applied to intact animals under more natural conditions to ascertain the degree to which the quasi-emotional states match the conditions of real excitement. It was with these purposes in mind that the present investigation was undertaken.

METHODS. In order to bring about a destruction of the cortex without destruction of the basal ganglia we have made use of the Sherrington decerebrator, and also we have approached the brain by way of the orbits. When the decerebrator was employed it was necessary to slant the knife

well forward so as to remove chiefly the dorsal cortex and the frontal lobes. As a rule we have obtained more consistent results through the orbital approach. After both carotid arteries have been tied a pointed stylet, dulled at the end, is thrust through the upper inner quadrant of the right orbit and directed toward the posterior portion of the zygomatic arch of the left side. When the stylet has reached nearly to the left cranial wall of that region it is moved up and down in a plane slanting downwards and outwards. The movement is continued as the stylet is withdrawn, thus effectively destroying the left frontal lobe and left lateral cortex. The instrument is then similarly introduced into the left orbit, and the right frontal lobe and right lateral cortex are likewise destroyed. A *post-mortem* examination of the brain was made in practically all cases. The plane of section usually passed about midway through the orbital lobe, thence obliquely across to the opposite hemisphere, cutting through the genu of the corpus callosum and ablating 2 to 4 mm. of the thalamus, and emerged a few millimeters posterior to the Sylvian fissure. The region of the cat's cerebral cortex, found by Barenne (8) to subserve sensation, including pain, was thus quite disconnected from the rest of the brain. A wedge of the occipital cortex does not suffer direct injury. Usually there is no considerable amount of hemorrhage.

In some instances we wished to know to what degree the effects produced by the decortication just described could be obtained under decerebration. We found that the skull about 1 cm. dorsal to the posterior end of the zygomatic arch is sufficiently thin to permit the stylet to be thrust through it readily. By appropriate movement of the instrument after it has penetrated the brain case, the active pseudoaffective state can be quickly changed to a state of decerebrate rigidity.

In our experience all the operative procedures should be performed with the utmost rapidity in order that the period of anesthesia may be as short as possible. When the period of anesthesia is prolonged many of the phenomena to be described later do not occur. On the other hand, if the operation is begun as soon as ether has rendered the animal insentient, and if the ether is removed as soon as the swift cerebral ablation has been accomplished, there is usually a very good showing of the quasi-emotional phenomena.

The phenomenon related to the pseudoaffective state that we are reporting in this paper is secretion from the adrenal medulla. In testing the presence of increased and varying medulliadrenal secretion we have employed the denervated heart, the use of which for that purpose has been justified in previous papers (9). Fasting animals (cats) were selected, to make sure that the hepatic factor would play only a temporary and negligibly minor rôle in causing cardiac acceleration (10). Thus there was no delay due to abdominal operation. As an indication of the speed

with which the entire preparation can be made ready, when two skilled persons coöperate, we cite the following typical protocol:

October 15, 1924. Cat, male; 3.6 kilos.

- 10:27. Ether started
- 10:31. Right carotid artery tied and right vagus nerve cut
- 10:31½. Left carotid artery tied and left vagus nerve cut
- 10:32. Tracheal cannula inserted
- 10:33. Decortication *via* orbits. Ether stopped (used thereafter only to check movement during operation)
- 10:35½. Thorax opened and right stellate ganglion excised
- 10:37. Thorax opened and left stellate ganglion excised
- 10:39. Thorax closed
- 10:42. Right femoral artery exposed and cannula inserted
- 10:42½. Rectal thermometer introduced
- 10:43. First kymographic record taken

In this instance the period from starting anesthesia until a blood-pressure tracing was obtained was 16 minutes. Our shortest record was 14 minutes, our longest 22 minutes. Usually the procedures did not require more than 17 minutes.

As in previous cases in which the denervated heart has been employed to indicate medulliadrenal secretion, the temperature of the animal, as shown by a thermometer in the rectum, was maintained as nearly as possible within a variation of one degree Centigrade from the initial temperature.

RESULTS. When the operation is performed as described above there appears quite spontaneously a group of remarkable activities such as are usually associated with emotional excitement—a sort of sham rage. A complete list of these pseudoaffective phenomena which we have observed is as follows: lashing of the tail; vigorous arching of the trunk, and thrusting and jerking of the limbs in the thongs which hold them to the animal board, combined with a display of claws in the fore feet and clawing actions, often persistent; rapid head movements from side to side with attempts to bite; very rapid panting respiration, developing usually within 10 or 15 minutes after decortication and reaching a state precisely similar to that seen after great exertion or on being overheated (the mouth is held open, the tongue is moved rapidly to and fro, the nares widen synchronously with each breath; the breathing is very superficial and in eight cases in which it was recorded reached the remarkably high range of from 288 to 304 breaths per minute (e.g., see fig. 1)). These activities occur spontaneously, but in “fits” or periods, lasting from a few seconds to several minutes. During the intermediate quiet stages a “fit” may be evoked by slight handling, touching the paws or jarring the table. In the quiet periods some evidence of rigidity was usually found to be present, or could be obtained by bending the fore legs; when rigidity was marked, as in a few experi-

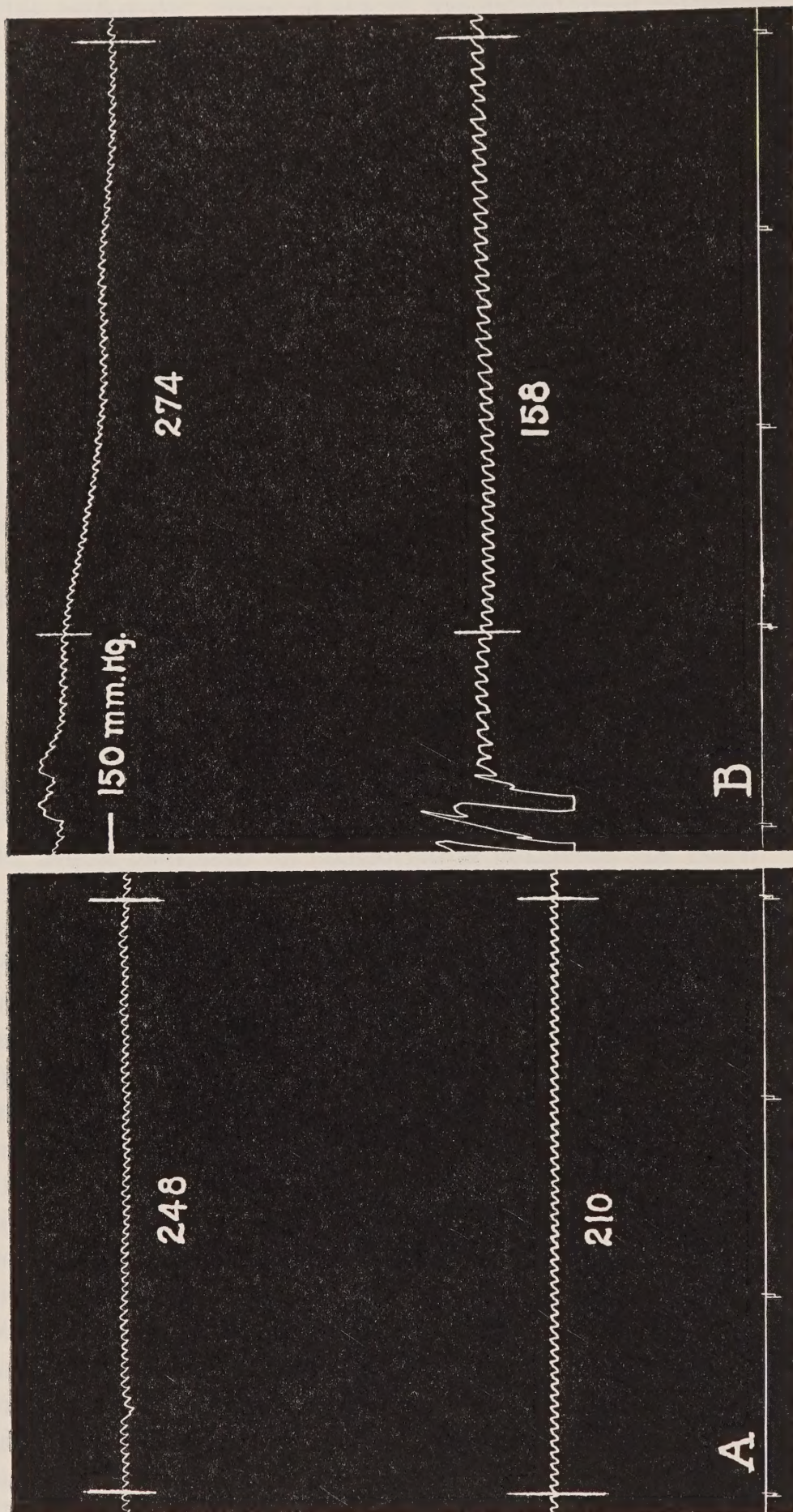


Fig. 1. Experiment of October 29. Record of blood pressure, cardiac and respiratory rates in the pseudofactive condition (original size). Base line registers zero blood pressure and time in 5-second intervals. A, 11:30, during quiet (heart rate, 248 beats per minute; respiration, 210 per minute); B, 11:32, immediately after activity (heart rate, 274 per minute; respiration, 158 per minute). Tail hairs erect, hind paws wet with sweat.

ments, and as happened not uncommonly in the late stages of experiments, the pseudoaffective features became correspondingly less pronounced.³

Besides the foregoing changes which involved skeletal muscle there were typical and more permanent visceral effects. Erection of the tail hairs,

TABLE 1

TIME	RECTAL TEMPERATURE	HEART RATE	BLOOD PRESSURE	RESPIRATION	NOTES
10:43	36.5	204	190		Animal quiet
10:50		188	160	80	Panting started. Hind toe pads moist, front pads dry
10:55		184	150	180	Clawing, tail slightly rough; hind toes wet; mouth open and tongue moved as in panting
10:59	37.5	180	150	216	Quiet
11:00		196	186	180*	Spontaneous activity
11:09		180	156	228	Quiet
11:10	37.2	200	170	140*	Activity—jerking and thrusting
11:15		180	160	288	Quiet: other conditions as at 10:55
11:20		178	140	276	Quiet
11:21	36.4	202	164	48*	Spontaneous jerking, raising of head, etc.
11:30		184	150	240	Quiet. Tail rough; hind toes wet; panting respiration
11:37					
11:51					Very light etherization to abolish reflex activity while both <i>adrenals</i> were removed
11:54	37.8	159	76	156	Quiet
12:0		156	90	86	Quiet
12:05		158	108	34	Toe pads not perspiring; tail slightly rough
12:20	38.3	160	108	26	No change of condition
12:30		156-158-154	100-110	25	Stimulation of exposed right femoral nerve for 30 sec.; respiration deepened
12:35		158-160-160	110-156-130-100		Stimulation of left brachial nerve for 30 sec.; great activity
12:40		158	90		Animal killed by clamping trachea with no change in heart rate during the asphyxia
12:50		158			

* The slower respiratory rate brought on by activity was quite characteristic (see also fig. 1).

³ Recent interest in the double innervation of skeletal muscle, and in the rôle of sympathetic nerves in the maintenance of its tone, makes appropriate the report that in many of our cases marked rigidity of the fore limbs was noted, although the stellate ganglia through which the sympathetic impulses to the fore limbs pass, had been completely removed.

which recurred again and again after they were smoothed down; sweating of the toe pads, in some instances so marked as to wet the hairs between the pads (this phenomenon was absent from the fore paws when the stellate ganglia were removed, and sometimes from the paw of the hind limb in which the femoral artery was closed); dilatation of the pupil so that during activity it might be three times as wide as during a preceding period of quiet (since the stellate ganglia had been removed the effect was probably largely due to inhibition of pupillo-constrictor impulses); micturition; contraction of the rectum, with expulsion of the rectal thermometer, and sometimes defecation; and a high blood pressure ranging from 146 to 210

TABLE 2

Changes of rate of the denervated heart, and maximal blood pressures, observed in the pseudoaffective state when the adrenal glands were intact

DATE	AT START OF EXPERI- MENT	HEART RATE PER MINUTE			MAXIMAL BLOOD PRESSURE
		Minimal during quiet	Maximal during activity	At end of experi- ment	
					<i>mm. Hg.</i>
September 25, 1924.....	224	220	232	*	168
September 27.....	274	273	308	*	210
September 30.....	212	204	256	*	146
October 3.....	256	255	276	228	180
October 3.....	260	212	230	*	168
October 14.....	234	228	248	204	172
October 15.....	204	178	202	184	190
October 22.....	256	242	270	212	190
October 23.....	196	188	256	176	204
October 24.....	208	182	212	184	186
October 25.....	211	184	240	191	160
October 27.....	268	232	248	212	194
October 29.....	254	248	274	204	160
October 31.....	248	222	256	212	206
November 1.....	274	264	272	212	195

* *Experiment interrupted.*

mm. of Hg. Like the pseudoaffective reflex phenomena described by Woodworth and Sherrington, these spontaneous reactions did not always appear in complete combination; occasionally several of them were absent either wholly or during a part of the experiment. In all cases we concluded the experiment by killing the animal; the preparations were usually studied from 1.5 to 3 hours.

Some of the points mentioned in the foregoing list, and also the evidence that there is increased secretion from the adrenal medulla in company with the other indications of sympathetic activity, will now be reported in detail.

In table 1 are presented the main facts of body temperature, heart rate, blood pressure and respiration at various times after the preparation had been made. The experiment was that of October 15, the operative procedures of which were detailed above (see p. 287). In table 2 are given the variations of heart rate and also maximal heights of blood pressure in 15 of our 19 experiments. The remaining 4 experiments were done by means of the Sherrington decerebrator, and because of accident or hemorrhage were unsatisfactory. Examination of table 1 brings out the fact that the rate of the denervated heart when the adrenal glands were present was well above the average rate which prevailed after they had been removed. In this case only a moderate instance of the general rule is illustrated. In previous studies in this laboratory the average rate of the denervated heart in a series of 20 fasting animals from which the adrenals had been removed was 156 beats per minute—a rate closely approximating that observed in the experiment detailed in table 1 after both adrenals had been extirpated. Comparison of this figure with the figures in table 2 reveals immediately a remarkable difference. The average minimal rate there reported during quiet was 222 beats per minute—66 beats above 156.

The rate of the denervated heart is usually high shortly after the decortication, it is likely to be lower thereafter during quiet periods, and it is seen to rise sharply during any exhibition of vigorous spontaneous activity (see tables 1 and 2 and also fig. 1). In the 15 cases in table 2 the average rate shortly after decortication was 239 beats per minute; it fell during quiet to 222, and rose during activity to 252 beats. The extraordinary rate of 308 beats per minute was recorded as the maximal rate during activity in one instance.⁴ The increase during activity is not seen if the hepatic nerves are cut and the adrenal glands are removed, or is slight if the adrenal glands are removed from fasting animals (see table 1, 12:35, when marked activity and a great rise of blood pressure were induced by stimulation of a brachial nerve). Since these high rates occur while the adrenal glands are present and active, and are replaced by rates in the neighborhood of 156 beats per minute after the adrenal glands have been extirpated, we draw the inference that the adrenal medulla participates

⁴ Tulgan (This Journal, 1924, lxi, 441) has declared that after bilateral vagotomy the heart rate is at its physiological maximum, and can not be increased by stimulation of a sensory nerve or by injection of adrenalin. In the figures he publishes the maximal rate for the cat is set down at 210 beats per minute. As shown in figure 1 and in table 2, this is not a "physiological maximum" in the sense that the heart is unable to beat faster than 210; it may beat very much faster than that. Furthermore, Cannon and Rapport (This Journal, 1921, lviii, 330) have recorded rates of approximately 260 beats per minute induced by injections of adrenalin. Does the denervated heart differ from the heart still innervated by the sympathetic (as was the case in Tulgan's experiments)? Does the nature of the anesthetic restrict the action of adrenalin?

in the general widespread discharge of sympathetic impulses in the pseud-affective state, and pours adrenin into the blood stream to such a degree that the denervated heart is driven for a considerable period, often two hours or more, to maintain a rapid beat. As shown in table 2, the rate toward the end of the experiment is likely to be considerably less than at the beginning. This change does not appear to be due to a diminution of the quasi-emotional activity; it is possibly the consequence of exhaustion of the adrenal medulla, but we have not determined that point.

As table 2 reveals, the maximal blood pressure is high in these cases. Rarely does the normal blood pressure of the cat under ether anesthesia range above 150 mm. Hg (11). In all but one of the cases listed in table 2 the pressure went well above that figure. One might suppose that the high blood pressure might be due to increased intracranial pressure resulting from the operation. We have observed, however, blood pressure as high as 190 mm. Hg in an animal in which the pseudoaffective state was brought on by a Sherrington decerebration. The opened cranium in this case would not permit the development of a high cerebral pressure. Furthermore, the absence of any considerable hemorrhage in cases in which orbital decortication was employed would hardly warrant the supposition that a considerable intracranial pressure developed.

It was noteworthy that both the blood pressure and the rate of the denervated heart were highest in animals in which the pseudoaffective phenomena were most prominent. If the decortication failed to produce the physiological signs of emotional disturbance, but rather the indications of decerebrate rigidity, the heart rate was invariably lower. Or if by further sectioning at the mid-brain the preparation was changed from the quasi-emotional state to a state of rigidity, the denervated heart beat more slowly. The average minimal rate in nine cases when the condition of rigidity was prominent was 198 beats per minute, and in six cases in which activity was replaced by rigidity after further section through the mid-brain the average rate quickly fell from 234 to 210 beats per minute. The rates in the rigid state, as will be noted, are higher than the rate seen after removal of both adrenal glands (156 beats per minute) but not nearly so high as during the active periods of a quasi-emotional exhibition (252 beats per minute). It is clear, therefore, that although medulliadrenal secretion is stimulated by the experimental circumstances which prevail in decerebrate rigidity it is stimulated still more during the pseudoaffective responses.

DISCUSSION. The results presented in the foregoing paragraphs bring support to earlier evidence that there is a true emotional secretion from the adrenal medulla. This evidence, first reported by Cannon and de la Paz (12) in 1911, was confirmed the next year by Elliott (13), who found that cats excited by new experiences in the laboratory had a smaller adrenin

content in the adrenal medulla than did quiet animals, that if the splanchnic nerves had been cut previously on one side the adrenal medulla on that side had a larger load of adrenin than did the other gland after the animals had been excited by morphia or β -tetrahydronaphthylamine, and that if the superior cervical ganglion were removed a paradoxical dilatation of the pupil occurred when the animal became angry, a reaction which failed after both adrenal glands were excised. The last of these three lines of evidence was strengthened by similar observations by Kellaway (14). Stewart and Rogoff (15) were unable to note the effects seen by Kellaway when they removed one adrenal gland and denervated the other, and they found no reduction of the adrenin content of the medulla in animals subjected to excitement. Our present observations are in harmony with the testimony of Elliott and of Kellaway and not with that submitted by Stewart and Rogoff.

A noteworthy feature of our results is the markedly faster rate of the denervated heart which appeared whenever the animal changed from quiet to aggressive activity, and the absence of that effect if the adrenal glands had previously been removed (see table 1). It would appear from the observations of Hartman, Waite and Powell (16) that any considerable muscular movement which an animal engages in is associated with increased medulliadrenal secretion. Unpublished observations made in this laboratory may be given a similar interpretation. Our results indicate that even when in an emotional state the adrenal medulla is hyperactive, the putting forth of vigorous muscular effort is associated with a still greater activity and a larger outpouring of adrenin—causing an increase of heart rate, on the average, from 222 to 252 beats per minute. These facts suggest that the somatic neuromuscular functions more or less under voluntary control, and the visceral or non-voluntary functions, that are brought into action simultaneously during excitement, are affected to a similar degree. The interesting question is raised whether inhibition of the somatic expressions of emotional disturbance may not be accompanied by a correspondingly smaller expression of the visceral functions. The control of one's behavior when there is danger that expression may be excessive may have more than superficial effects.

The facts reported in the foregoing paragraphs are merely the first results of a series of studies which we are making on the pseudoaffective preparation. It is hoped that the methods and results established by study of this preparation can be tested under more natural conditions in intact animals and in man.

SUMMARY

A preparation is described in which many of the physiological accompaniments of great emotional excitement can be produced in an acute experiment, without anesthesia, and thus can be readily studied for hours.

The denervated heart in this preparation has rates averaging (in 15 experiments) 222 beats per minute during quiet, and 252 beats per minute during activity. If the adrenal glands are removed the rate of the denervated heart averages 156 beats per minute, and is not increased to a noteworthy degree (not more than 4 to 8 beats per minute) during activity. We draw the inference that associated with the physiological signs of emotional excitement in the pseudoaffective state there is greatly increased secretion of adrenin from the adrenal medulla.

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